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Pentachloronitrobenzene (PCNB)
Position Document 1

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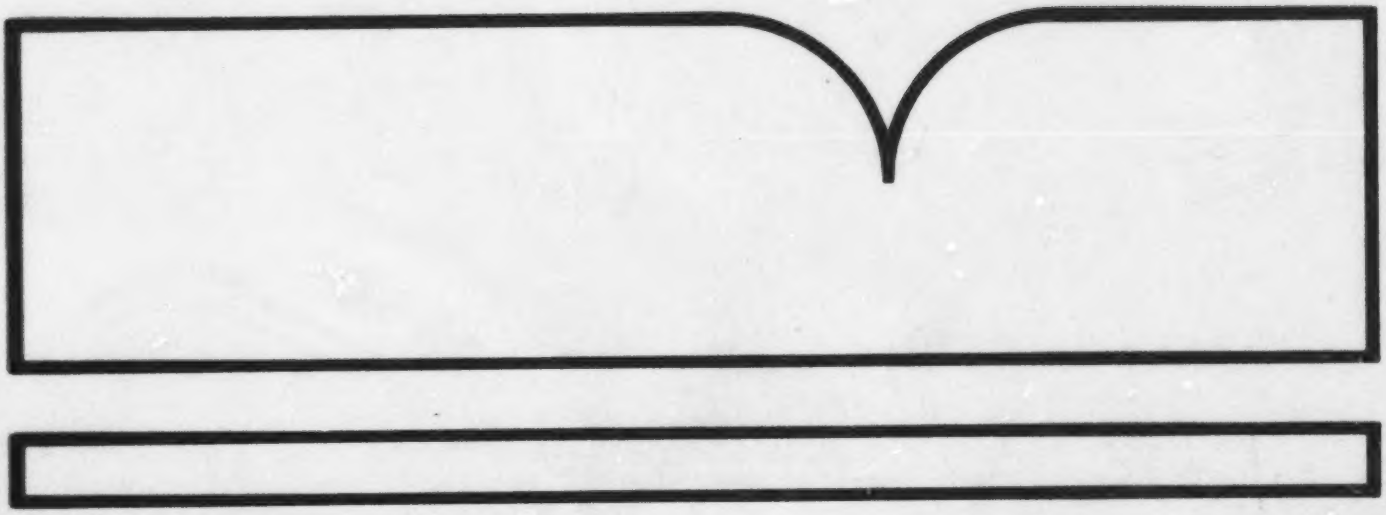

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EPA/SPRD-80/49

EPA Working Group on PCNB
Environmental Protection Agency

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Pentachloronitrobenzene (PCNB): Position Document 1

I. BACKGROUND

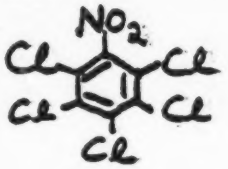
A. Characteristics of PCNB

(1) Nomenclature

PCNB is the common name for pentachloronitrobenzene. Other common names are quintozene and terrachlor. Some trade names for PCNB are Avicol, Botrilex, Brassicol, Folosan, Terraclor and Terrachlor. In many products PCNB is combined with other active pesticidal ingredients, such as captan, terrazole, phorate, maneb, thiram, zineb, disulfoton and others.

(2) Chemistry

Technical grade PCNB consists of about 98% PCNB and 2% related compounds such as hexachlorobenzene, tetrachloro-nitrobenzene, and pentachlorobenzene. These and otehr metabolites are shown in figure 1. The molecular weight is 295.4. The molecular formula is $C_6Cl_5NO_2$. The structural formula for PCNB is:

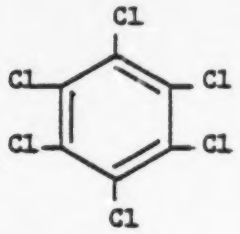


PCNB is a crystalline solid, pale yellow to white, depending on purity, with a musty odor. Its density is 1.718 at 25°C, its boiling point is 328°C at 760 mm Hg and its melting point is 142 -145°C. Some vapor pressures are:

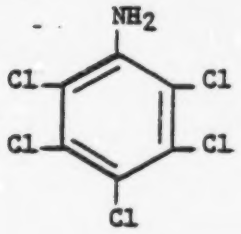
1.61×10^{-5} mm Hg at 10°C

5.0×10^{-5} mm Hg at 20°C

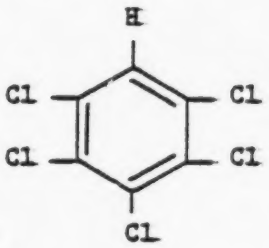
11.3×10^{-5} mm Hg at 25°C



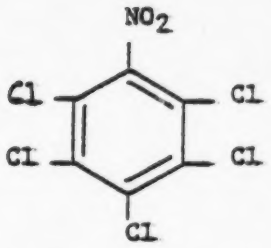
hexachlorobenzene
(HCB)



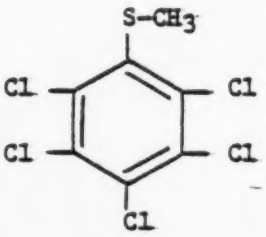
2,3,4,5,6-pentachloroaniline
(PCA)



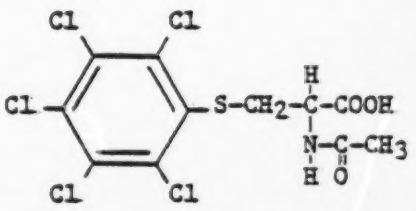
2,3,4,5,6-pentachlorobenzene
(PCB)



2,3,4,5-tetrachloronitrobenzene
(2,3,4,5-TCNB)



S-methyl pentachlorophenyl sulfide
(MPCPS)



N-acetyl-S-pentachlorophenyl-L-cysteine

Figure 1. Chemical structures of PCNB impurities and various PCNB metabolites

PCNB is freely soluble in carbon disulfide, benzene, chloroform, ketones, and aromatic and chlorinated hydrocarbons, and is slightly soluble in alkanols. It is nearly insoluble in water (0.44 mg/l at 20 degrees C.) and in ethanol (2 mg/l at 25 degrees C).

(3) Degradation, Transport and Soil Residues

Chacko et al. (1966) found that eight soil fungi species and nine actinomycete species, grown in nutrient media in vitro, degraded PCNB to pentachloroaniline (PCA). In one species of fungus, Nakanishi and Oku (1969) found that PCNB was metabolized to PCA and pentachlorothioanisole (PCTA). Sevral authors have stated that microbial degradation of PCNB occurs only when the microorganisms are actively growing (Casely 1968, Ware and Roan 1970, Chako et al. 1966).

Caseley (1968) traced the disappearance of PCNB from Yolo fine sandy loam through biological and non-biological pathways. He analyzed only for PCNB and not for its metabolites. Sterilized and unsterilized soil samples were measured for PCNB loss under moisture conditions of 3%, 20% and 50% (equivalent to air dry, field capacity and saturated soil, respectively). It was found that only 10% of the PCNB excaped from the air-dry soil; 20% and 50% escaped from the moister field-capacity and saturated soil samples, respectively. From these results the author observed that an increase in soil moisture increases the mobility of PCNB in the soil and thus increases losses through volatilization.

In the unsterilized field-capacity samples, 80% of PCNB was lost after 10 months. Three-fourths of this loss was to the water-saturated air passed over the sample and one-fourth to microbial degradation. Undegraded PCNB was the major component of the removed air stream. The author conluded that "considerable quantities" of PCNB could be lost to the air in intensively cropped areas where irrigation is used.

Ko and Farley (1969) attempted to confirm the conversion of PCNB to PCA in soil. Residues of PCNB were measured in moist soil, sterilized-moist soil, submerged soil and sterilized-submerged soil. Only in the submerged soil did PCNB disappear (56% after 3 weeks); more than

half of this amount was transformed into PCA. The authors concluded that this conversion resulted from soil microorganisms. They suggested that the remaining PCNB was lost through a nonbiological process, since the same amount disappeared from the sterilized-submerged soil.

Wang and Broadbent (1972) measured the rate of loss of PCNB from three California soils--Colombia fine sandy loam, Sacramento clay and Staten peaty muck. PCNB was found to have a half-life of 4.7, 7.6 and 9.7 months, respectively, in these soils. Kaufman (1970) confirmed that the conversion of PCNB to PCA is enhanced by submergence of treated soil in water.

The EPA National Soils Monitoring Program reports that in 1972 there were no detections of PCNB in any of 1,487 samples from 37 states (Memo, 1976). Of the 1,487 samples collected in 1973, only 3, or 0.3%, had detectable levels of PCNB. Residues ranged from 0.22 to 2.61 ppm. Pesticide applications had been made at seven of these sites in 1973 (0.5% of 1402 responses) with an average total application of 0.02 lb/A (0.02 kg/ha).

(4) Bioaccumulation and Metabolism

(a) Plants

Casanova and Dubroca (1973) studied the residues of PCNB found in lettuce after treatment of the soil with PCNB. In the first set of experiments, PCNB was applied to the soil before planting at rates of 15 and 30 kg AI/ha. Residues were determined by gas chromatography after 12 weeks of growth. Table 1 gives the results of the residue tests.

Table 1. Residues of PCNB in lettuce leaves (ppm) from plants grown in treated soils

	Soil Treatment rates, kg AI/ha		
Study location (in France)	0 kg	15 kg	30 kg
Nantes	0.51	0.63	1.10
Rennes	0.17	0.52	1.05
Nantes	0.05	0.47	1.15
Rennes	0.07	0.61	1.10
Rennes	0.10	0.16	0.43
Average	0.18	0.48	0.96

The residues after the application of 15 kg AI/ha were approximately 0.5 ppm, while the residues after an application of 30 kg approached 1.0 ppm, the established tolerance for PCNB in France. The authors suggest that this was due to PCNB applications prior to the study.

In the second set of experiments, the same application and test methods were used, except that analyses for HCB, an inherent contaminant of PCNB, were included and residues were determined not only in lettuce but also in soil before treatment and at the end of the growing season. The results are given in Table 2. The results of the first test were confirmed in the second test, which showed the presence of PCNB residues in lettuce at about 1.0 ppm after an application of 30 kg AI/ha. Residues of HCB from the same application were considerably lower than these values; they ranged from 0.02 in lettuce from untreated soils to 0.04 ppm in lettuce from treated soils.

Table 2. Residues of PCNB and HCB in lettuce from treated soil (ppm)

		Soil Treatment Rates, kg AI/ha					
		None		15 kg		30 kg	
Location	Procedure	HCB	PCNB	HCB	PCNB	HCB	PCNB
Nantes	Lettuce	0.016	0.29	0.034	0.83	0.041	1.04
	Soil (pre-plant)	0.160	1.50	0.160	1.50	0.160	1.50
	Soil (at harvest)	0.170	1.57	0.620	20.90	2.07	82.41
Rennes	Lettuce	0.025	0.34	0.43	0.66	----	----
	Soil (pre-plant)	0.080	0.64	0.090	0.90	----	----
	Soil (at harvest)	0.087	0.67	0.660	10.27	----	----

Residues in soil before treatment varied considerably with the study location. HCB residues also varied, but they were consistently lower than the PCNB residues.

Casanova and Dubroca (1973) attempted to show that residues found in lettuce were a result of absorption from soil through roots rather than from surface contamination. In

a laboratory, soil was treated with the equivalent of 15 and 45 kg AI/ha PCNB. Residue measurements were taken 8 weeks later. Table 3 shows the resulting residues.

Table 3. Residues of PCNB and HCB in soil and lettuce (ppm)

	Soil Treatment Rates, kg AI/ha					
	None		15 kg		45 kg	
Nature of test	HCB	PCNB	HCB	PCNB	HCB	PCNB
Treated soil	N.D*	0.14	0.50	20.40	1.86	69.10
Lettuce	N.D*	0.03	0.01	0.73	0.02	1.56

* N.D.= undetected

Kuchar et. al. (1969) studied the metabolism of PCNB in immature cotton plants. Cotton plants grown in soil containing 300 ppm of PCNB were monitored for PCNB, its impurities and its metabolites. Results after two weeks growth (roots included) were:

Component	Residues (ppm)
PCNB	155.0
PCB	3.96
TCNB	0.018
HCB	4.61
PCA	1.11
MPCPS	2.95

PCA had been found in young corn and soybean plants grown in PCNB-treated soil (Kuchar et al. 1969). Gorbach and Wagner (1967) have also cited PCA as a metabolite in potatoes, along with two unidentified metabolites. Kuchar et al. (1969) later described these unidentified substance as having gas chromatograph retention times identical to HCB and MPCPS.

HCB applied to wheat seed is translocated to the developing grain (Johns 1969, Smith 1969).

(b) Animals

Rabbits - In a study conducted by Betts et. al. (1955) 12 rabbits received either 1, 2, or 3 g of PCNB via stomach tube. Urine and feces were collected for 72 hours. An average of 62% of the administered dose was found in the feces from the 2 g dose and was considered unabsorbed. Another 11% of the dose could be accounted for as PCA in the urine. N-acetyl-S-(pentachlorophenyl)-L-cysteine was also isolated from the urine at a level 14% of the initial dose. Pentachlorophenol was formed only in trace amounts.

To determine the metabolic pathways of 2,3,4,5-TCNB, 0.7 g was administered to rabbits as an aqueous suspension via stomach tube. The 2,3,4,5-TCNB was poorly absorbed; 33% was found in the feces after 48 hours. Further, 11% of the dose was excreted in the urine as 2,3,4,5-tetrachloroaniline (2,3,4,5-TCA). The excretion of the glucuronide (41%) and the ethereal sulfate (6%) of 6-amino-2,3,4,5-tetrachlorophenol indicated that ring hydroxylation had occurred (Bray et al. 1953).

Dogs - Purebred beagles, approximately 4.5 months old (4 per sex per dose), were fed 0, 5, 30, 180 or 1,080 ppm PCNB in their diets for two years (Borzelleca 1971). Olin technical grade PCNB (97.8%), containing 1.8% HCB, 0.4% 2,3,4,5-TCNB and 0.1% PCB, was used. Kidney, brain, skeletal muscle, liver, spleen fat, bile, blood urine and feces samples were collected for analysis after two years. Electron-capture gas chromatography was used to detect the presence of PCNB, PCB, HCB, PCA and MPCPS. Results for liver, kidney, fat and feces at dose levels of 0, 5, 30, and 180 ppm dietary exposures are summarized in Table 4.

MPCPS appeared to have an equal propensity to store in either the fat or skeletal muscle of the male rat. At the method's sensitivity level (unstated), a 60 day withdrawal period from the treated diet resulted in undetectable residues of PCA, MPCPS and PCB in adipose tissue at all exposure levels. Substantial residues of HCB remained from all levels of dietary exposure.

Table 4. Dog tissues and excreta concentrations of PCNB, its metabolites (PCA, MPCPS), and related impurities(a) after 2 years on diet.

Tissue	Diet	Concentrations found (ppm) PCNB	PCA	MPCPS	PCB	HCB
Liver	0	ND	<.06	<.05	<.02	ND
	5	ND	<.06	<.05	<.02	0.039
	30	ND	<.06	<.10	<.02	0.125
	180	ND	<.06	<.05	0.54+0.61	0.74
Fat	0	ND	<.08	<.03	.005	.005
	5	ND	<.08	<.03	.093	.452
	30	ND	<.08	<.03	.163	1.11
	180	ND	<.08	ND (b)	.767	6.12
Kidney	0	ND	ND	ND	<.03	ND
	5	ND	ND	ND	<.03	<.04
	30	ND	ND	ND	<.03	<.10
	180	ND	.018(c)	.021	<.10	<.60
Feces	0	0.004	.005(c)	.014(d)	ND	0.004 (c)
	5	0.059	.188	.134	.007	0.009
	30	0.343	.450	.675	.03	0.022
	180	1.56	1.96	.192	.03	0.072

(a) PCNB, 97.8%; HCB, 1.8%; PCB, 0.1%; 2,3,4,5-TCNB, 0.4%.
(b) two of three samples.
(c) one dog, ND in two.
(d) average two dogs, ND in one.

Rats - Finnegan et al. (1958) conducted an initial study to determine the amount of PCNB stored in the fat of male and female albino rats. The diets contained 0, 63.5, 1,250 or 2,500 ppm of PCNB as a 25% dust. The animals were fed for 3 months and then sacrificed. The results showed a dose-related increase in content of PCNB in adipose tissue. Subcutaneous and perirenal fat samples were taken to be analysed by neutron activation of chlorine. For the respective dietary levels, the average chlorine concentration in ether extracts of fat was 42.4, 392, 571 and 1,151 ug/g in males, and 43.7, 470, 875 and 1,316 ug/g in females.

As stated by Kuchar et al. (1969), the neutron activaton process was later found to be inadequate for determining residues of PCNB or its metabolites in animals.

A subsequent study by Borzelleca et al. (1971) stated that the residue in the fat orignally identified as PCNB consisted mostly of the impurities PCB and HCB.

As part of a reproduction study (Borzelleca et al. 1971), a portion of F-2b generation rats were fed diets containing 0, 5, 50 or 500 ppm PCNB for approximately 3 weeks following weaning. The animals were sacrificed after producing two litters. Analyses were made of composites of tissue and excreta from three rats of the same sex and dietary level. Those animals that were not sacrificed at this time were returned to control diets for two months. Residues of PCNB, HCB, PCB, PCA and MPCPS were found in skeletal muscle, liver, kidney, fat and feces at the end of the 33 week feeding period and two months after withdrawal from treated diets (see Table 5).

The major tissue of storage appeared to be adipose tissue (fat) where both PCB and HCB displayed dose-related storage levels. This storage trend continued to the 1,080 ppm exposure level, where respective storage levels of PCB and HCB increased to 5.15 and 194 ppm, respectively. No significant amounts of any product, including PCNB, were found in the urine. Decreased elimination of HCB from animal tissues over an extended time period was indicated by dose-related levels of HCB in fecal matter at the end of the 60 day withdrawal period.

Table 5. Rat tissue and excreta concentrations of PCNB, its metabolites, (PCA, MPCPS) and related impurities (PCB, HCB)

Specimen	Diet (ppm)	Days on control diet(a)	Sex	Conccentrations found (ppm) PCNB (b)	PCA	MPCPS	PCB	HCB
Sk. Muscle	500	0	M	ND	0.117	8.13	0.042	29.7
Liver	500	0	M	ND	0.069	0.306	0.010	1.93
Kidney	500	0	M	ND	0.084	0.269	0.131	6.43
Fat	5	0	M	ND	ND	0.060	<.001	0.587
	5	0	F	ND	ND	0.055	<.001	0.824
	50	0	M	ND	0.019	0.46	0.019	10.8
	50	0	F	ND	0.095	0.345	0.011	4.73
	500	0	M	ND	1.11	4.74	0.304	117
	500	0	F	ND	0.238	3.82	0.176	49
	5	60	M	ND	ND	ND	ND	1.07
	50	60	M	ND	ND	ND	ND	3.67
	500	60	M	ND	ND	ND	ND	22.3
Feces	5	60	M	ND	ND	ND	ND	0.023
	50	60	M	ND	ND	ND	ND	0.137
	500	60	M	ND	0.027	0.101	ND	1.95

(a) after 33 weeks on test diets
(b) ND = none detected

Cows - PCNB (Olin technical grade) was dissolved in corn oil and administered orally in gelatin capsules to cows (Borzelleca et al. 1972). Doses for each cow were dependent upon the animal's consumption of feed the previous week. Three cows per dose level received 0, 0.1, 1.0 or 10 ppm PCNB for 12 to 16 weeks. Fat biopsies for analyses during the course of the study were collected from the brisket area; additional tissues were obtained at autopsy. The cows were milked twice daily. An aliquot was removed and analyzed by a gas chromatograph equipped with electron capture. Levels of detectability for control and treated samples differed from week to week; consequently, the results are difficult to assess accurately. Tissue samples included skeletal muscle, liver, kidney and abdominal and subcutaneous fat.

Considerable variation in residue levels was noted when individual samples were analyzed. Levels of HCB in milk from cows fed a diet of 1 ppm PCNB ranged from .001 to .003 ppm between the twenty-first and fifty-sixth days of continuous exposure. The average value was .002 ppm. At a dietary level of 10 ppm PCNB, the HCB residue ranged from non-detectable to .015 ppm, with an average value of 0.01 ppm. Levels of PCNB, PCA, MPCPS and PCB showed sporadic variation, but were generally .005 ppm or less. There was little indication of dose-related level changes.

Samples of subcutaneous fat biopsied at 0, 1, 2, 4, 7 and 8 weeks after exposure to 10 ppm in the diet suggested a 0.5 ppm plateau of HCB residue beinning in the fourth week and continuing through the eighth week. PCA appeared to stabilize at a level of about 0.1 ppm between weeks 1 and 8 at the 10 ppm dietary exposure level. The remaining residues (PCA, PCNB and MPCPS) were negligible or non-detectable.

Goursaud et al. (1972) studied the relationship of HCB residues in endive roots to residue level of HCB in the milk of cows eating the roots. First they determined that only PCNB was chemically related to HCB. Using gas chromatography, they found that the roots of the endives were contaminated with both HCB and PCNB and that the milk of cows eating these endives was contaminated with HCB. The most contaminated milk (26 ppm HCB) was from cows receiving 25 to 30 kg of endive roots per day. The roots were contaminated with 0.11 ppm of HCB. Another sample of milk containing 0.13 ppm of HCB came from a cow receiving endive roots contaminated with 0.006 ppm HCB.

In a subsequent study (Goursaud et al. 1972), 2 cows received a feed mixture containing 12 kg of endive roots contaminated with 0.16 ppm HCB and 2.16 ppm PCNB. The residues found in the milk are shown in Table 6. The authors concluded that the HCB contamination in the milk was linked to the application of PCNB to endives. They speculated that the source of HCB was from original formulation rather than from PCNB degradation.

Table 6. Residues of HCB and PCNB (ppm) in milk of cows fed treated endive roots

Milk sampling day	HCB	PCNB
0*	0.21	Negligible for all samples
1	0.57	
2	1.23	
3	1.34	
4	1.68	
5	1.83	
6	2.00	
7	2.02	

* - Day 0 means the day before the root-feed mixture was fed to the cows.

Feeding studies have shown that HCB is assimilated in the fat and other tissues of sheep (Craig and Dwyer 1961, Avrahami and Steel 1972a), chickens (Craig 1959, Watts 1968a, 1968b, Avrahami and Steel 1972b, 1972c), pigs (Gardner and Armstrong 1960, Hansen et al. 1977), Japanese quail (Vos et al. 1968, 1971), kestrels (Vos et al. 1972), lambs (EPA 1976), rats (Medline et al. 1973, Villenueve 1975, Kuiper-Goodman et al. 1977) and aquatic organisms Laseter et al. 1976, Isensee 1976).

Field studies have reported the occurrence of HCB residues in fish (Zitko 1971, Koeman et al. 1972, Holden 1973, Johnson et al. 1974), poultry products (Stanhope 1969, Tuinstra and Roos 1970, Goursaud et al. 1972, Smyth 1972), birds (Gilbertson and Reynolds 1972, Zitko and Choi 1972, Cromartie et al. 1975, Nickerson and Barbehann 1975, White 1976, White and Heath 1976), edible animal tisues (Booth and McDowell 1975) and human milk and tissues (Bick 1967, Acker and Schulte 1970, Abbott et al. 1972, Siyali 1972, Brady and Siyali 1972, Curley et al. 1973, Neuhaus et al. 1973, Graca et al. 1974, Stacey and Thomas 1975, EPA 1977).

(5) Tolerances and Food Residues

Before any pesticide or any inert ingredient of a pesticide formulation may be used on a food or feed crop, a tolerance or exemption from a tolerance must be established. A tolerance is defined as the maximum residue level allowed for a particular pesticide on a raw agricultural commodity or a processed food or feed. It is based on the maximum residue expected from the proposed use and on the toxicological data submitted by the registrant. PCNB tolerances are summarized in Table 7.

Table 7. U.S. Tolerances* for PCNB on Raw Agricultural Commodities (40 CFR 180.291)

Crop	ppm	Crop	ppm
Bananas	0.1	Cottonseed	0.1
Beans	0.1	Garlic	0.1
Broccoli	0.1	Peanuts	1.0
Brussel sprouts	0.1	Peppers	0.1
Cabbage	0.1	Potatoes	0.1
Cauliflower	0.1	Tomatoes	0.1

* All tolerances are interim except for cottonseed.

FDA Market Basket surveys from 1964 to 1969 detected very small residues of PCNB in only 0.7% of leaf and stem type vegetables sampled. Residues ranged from 0.005 ppm to 0.42 ppm, with an average of 0.01 ppm (Duggan et. al. 1971). In the Market Basket Survey between June, 1971, and June, 1972, trace residues were found in only one sample (oil, fat or shortening). HCB residues ranged from 0.002 to 0.011 ppm in 4 composite samples, while PCA residues were found from 0.005 to 0.023 ppm in 3 composite samples (Manske and Johnson 1975).

In another FDA survey for 1973-1974, individual items in the dairy and meat composites in four market baskets were analyzed. PCNB residues occurred from 0.002 to 0.005 ppm in 7 composites. HCB ranged from 0.0003 to 0.0070 ppm in 17 composites. PCA was found from 0.004 to 0.050 ppm in 10 composites. TCNB occurred at 0.001 to 0.284 ppm in 8 composites (Manske and Johnson 1977).

Samples from FDA compliance and surveillance programs during 1972-1976 showed small residues in animal feed, vegetables and cottonseed meal (U.S.F.D.A. 1976).

HCB has been shown to survive the milling process of wheat and remain in the final product (Old 1969). It has also been detected at 0.010 ppb in raw and 0.006 ppb in finished U.S. drinking water (Murphy 1975).

(6) Toxicity

(a) Acute

Rats - The oral LD-50 for technical grade PCNB (Olin product) as a 10% solution in corn oil was found to be 1.71+/-0.17 g/kg for females (Finnegan et al. 1958). The oral LD-50 of a 75% wettable powder commercial formuation (Olin product) administered as a 40% aqueous suspension to male rats was greater than 12 g/kg.

Dogs - Groups of 10 mongrel dogs were administered PCNB (Olin product) via gavage as a 10% solution in warm corn oil. Doses up to 2.5 g/kg did not produce any deaths, although half of the dogs on this dosage level vomited (Finnegan et al. 1958).

Rabbits - Percutaneous toxicity was tested in male albino New Zealand rabbits weighing an average of 1.96 kg (Borzelleca et al. 1971). Animals with intact and abraded skin were used. The hair was removed from the trunk with an electric clipper and abrasions were made with a metal grid. The rabbits were restrained in stocks for 24 hours. PCNB (Olin product) was dissolved in dimethyl phthalate as a 30% solution and applied over the trunk under the restraining device. Doses of 10.0 ml/kg and 13.3 ml/kg were applied to 10 rabbits with intact skin and 13.3 ml/kg was administered to 10 rabbits with abraded skin. During the 14 days following dosing there were no indications of toxicity or skin irritation.

(b) Subacute

Rats - Five groups of 7 male and 7 female albino rats of weanling age were divided into separate groups for a 3 month study. Each was fed a diet containing 1 of 5 levels of PCNB (Olin Product) at 0, 63.5, 635.0, 1,250, 2,500 or 5,000 ppm. The animals were weighed at weekly intervals and a hematologic study was done upon termination of the study. Body weights for males were significantly depressed at the 2,500 ppm level. The males and females on

the 5,000 ppm level were killed at the end of 2 weeks. At the 1,250 and 2,500 ppm levels, the kidney-to-body weight ratios showed a significant increase for male rats. Significant increases in the liver-to-body weight ratios were found at all levels except in the females fed 63.5 ppm (Finnegan et al. 1958).

Rats (10 per sex per dose) were fed technical PCNB (purity and source unknown) in their diets at rates of 0, 1,000, 5,000, or 10,000 ppm for 90 days. The growth rate of rats fed 5,000 ppm PCNB was slightly less than that of controls. Rats on the 10,000 ppm diet had an even lower growth rate (FAO/WHO 1970).

Dogs - Groups of 3 mongrel dogs were placed on diets containing either 25, 200 or 1,000 ppm PCNB for 1 year. The PCNB (Olin product) was added as a dust formulation consisting of 20% PCNB, 77% Pyrax ABB and 3% Armour "Sticker." The dogs were weighed at weekly intervals and hematologic studies were make at the start, mid-point and termination of the study. The PCNB did not inhibit growth or result in any significant hematological or histopathological changes (Finnegan et al. 1958).

(c) Chronic

Rats - Finnegan et al. (1958) conducted a 2 year study in which rats in groups of 10 males and 10 females were fed a diet containing 0, 25, 100, 300, 1,000 or 2,500 ppm PCNB. The PCNB (Olin product) was the same formulation as for the dog experiment discussed above. Rats were housed individually and weighed weekly. They were given hematologic examination during the eleventh and twenty-fourth months of the experiment. Deaths did not correlate with the dose of PCNB. Female rats showed a slight growth suppression at 100 ppm and above. The growth of male rats accelerated, expecially at 25 ppm. Hematological values were within normal ranges. Lung abscesses and fatty changes in the liver did not correlate with PCNB dose.

Dogs - In a study conducted by Farbwerke Hoechst AG (cited in FAO/WHO 1970), groups of 6 dogs, 3 males and 3 females, were fed diets containing 0, 500, 1,000 or 5,000 ppm PCNB (purity not specified) for 2 years. Liver changes occurred in all groups and the degree was dose related. The 5,000 ppm level produced fibrosis, narrowing of hepatic cells, thick leucocyte infiltration and increased size

of the periportal areas. At the 500 and 1,000 ppm levels, the changes were similar but to a lesser degree. The highest dose level also produced atrophy of bone marrow and reduced hematopoiesis.

In another study (Borzelleca et al. 1971), prebred beagles, approximately 4.5 months old. were fed a diet containing PCNB (Olin product) at 0, 5, 30, 180 or 1,080 for 2 years. Hematocrit values showed a significant decrease at 18 months for males receiving dosages of 30 and 180 ppm. There was no change for males at 1,080 ppm. There were no dose related effects on urine analysis, blood chemistry, mortality, body weight, food consumption or the estrus cycle. A ratio of organ-to-body weight data showed a significantly greater value for livers of the dogs at 1,080 ppm PCNB. No treatment-related lesions were observed in dogs sacrificed at 1 year. In dogs sacrificed after two years, cholestatic hepatosis with secondary bile nephrosis was found in those dosed at 180 ppm and 1,080 ppm. Although these correlated with dosing, the authors considered the lesions reversible.

B. Registered Uses and Supplies

(1) Products

PCNB, a versatile fungicide, is an active ingredient in 233 Federally-registered products and 98 State-registered products. It is not used as inert ingredient in any registered products. PCNB is formulated as wettable powders, dusts, emulsifiable concentrates, granules, and in combination with other active ingredients previously listed.

(2) Use Patterns

295,000 pounds of PCNB were used as a soil fumigant in 1971; 7,000 pounds were used for seed treatment (EPA 1976). Of the soil fungicide applied, 77% was used on cotton, 19% on peanuts, and 4% on nursery and fruit crops, and vegetables. It is unlikely that PCNB is used on more than 12% of the total U.S. cotton acreage and 2%-3% of the U.S. peanut acreage (EPA, 1976).

C. Supply

The sole manufacturer of PCNB is the Olin Chemical Corporation of Stamford, Connecticut. In 1971 annual production was 3 million pounds active ingredient (National

Academy of Sciences 1975). According to the Olin Corporation, about a quarter of its production is exported. The U.S. Department of Agriculture has not recorded any imports.

II. REGULATORY HISTORY

A. Past Actions

On January 14, 1959, a registration for Technical Grade PCNB (EPA Reg. No. 1258-517) was issued to Olin Mathieson Chemical Corporation. This later became the Olin Chemical Corporation, the current holder of the PCNB technical registration. After the technical material was registered, numerous end use products were registered for various uses, including food crop uses. Tolerances for PCNB were set at zero.

In June, 1965, the National Academy of Sciences National Research Council issued a report recommending that "no residue" and "zero tolerance" concepts be abandoned. The report stated that zero tolerances were not desirable, since, as experience bore out, residues might be present at levels below the current sensitivity of detection methods.

On April 13, 1966 a joint USDA-HEW statement for implementation of the recommendation was published in the Federal Register. The plan included discontinuation by December 31, 1967 of registrations involving residues on food or feed for which a tolerance or exemption were lacking. However, extensions were granted until December 31, 1970, if progress was being made toward showing that the registration could be continued without undue hazard to the public health.

In late 1967, PR Notice 67-10 informed registrants of the extension of certain no residue and zero tolerance registrations beyond December 31, 1967. A Federal Register notice of April 15, 1967 stated that registrations involving food or feed on a no residue or zero tolerance basis would be cancelled unless (1) FDA established finite tolerance or (2) a progress report were submitted to show studies were underway to support such tolerance. All registered uses of PCNB listed in the USDA Summary of Agricultural Pesticides (Compendium) were extended until January 1, 1969.

On September 4, 1968, a petition to establish tolerances on several crops was received by the Federal Food and Drug Administration (FDA). This petition was filed (i.e. accepted) on September 11, but on October 20 was found to be inadequate. PCNB was certified for usefulness on alfalfa, celery, clover, beans, bananas, broccoli, brussel sprouts, cabbage, cauliflower, cottonseed, flaxseed, garlic, lettuce, mushrooms, peanuts, peppers, potatoes, and tomatoes on December 27, 1968.

PR Notice 69-2, issued on January 10, 1969, again extended affected registrations, beyond December 31, 1968 to January 1, 1970, based on the petition to FDA for uses in the USDA Summary. These include alfalfa, bananas, beans (all), beans (pole), beans (bush), broccoli, brussel sprouts, cabbage, cauliflower, clover, cotton, cotton (seed), garlic, lettuce (head), peanuts, peppers, potatoes, and tomatoes (staked, unstaked, and green house).

On February 18, 1969, this petition data was found sufficient to support the safety of the requested neligible residue tolerances (0.1 ppm) and 1 ppm on celery. On March 21 that year PCNB residue data and analytical methods were evaluated, and on August 1, the petition was amended by Olin Corporation. This amendment was evaluated on February 19, 1970.

PR Notice 70-1, issued on January 19, 1970 yet again extended registrations, this time beyond December 31, 1969. Some PCNB uses were extended to January 1, 1971; these uses are listed in the EPA Compendium of Registered Pesticides, which superceded the USDA Summary. PR 70-8, issued on March 10, 1970, informed registrants of further needs for toxicological information; specifically, carcinogenicity and teratogenicity studies were requested to be submitted or to be initiated for PCNB.

In March 1970, FDA recommended establishment of the proposed tolerances in spite of findings of possible tumorigenic and teratogenic effects by the U.S. Department of Health, Education and Welfare (DHEW 1969). A dissenting opinion from FDA, on the other hand, recommended further data requests because of these findings. Finally, on May 1, 1970, all uses under the amended petition were withdrawn because of an EPA requirement that the petitioner resolve the issues raised by DHEW. Later, on May 25, cottonseed was reinserted into the petition, and on February 17, 1971, a permanent tolerance was issued at 0.1 ppm.

In the meantime, on December 14, 1970 a new petition, was received by EPA. It proposed tolerances on peanuts at 1.0 ppm and bananas, beans, broccoli, brussel sprouts, cabbage, cauliflower, garlic, peppers, potatoes, and tomatoes at 0.1 ppm. Additional data was not submitted and thus EPA refused to file the new petition. In addition, since evidence did not support or was not submitted in support of PCNB uses on alfalfa, clover, and lettuce (head), these uses were cancelled while remaining uses were extended until further notice.

Olin requested on October 11, 1971, a reconsideration of the petition, since the World Health Organization (WHO) had established a temporary acceptable daily intake which was based on crop residue data in agreement with the proposed tolerances. As a consequence, on November 10, EPA filed the amended petition and on November 23 issued a Certification of Usefulness for 0.1 ppm on bananas, beans, broccoli, peppers, potatoes, and tomatoes and 1 ppm in or on peanuts. However, on February 23, 1972, EPA recommended against establishment of proposed tolerances and requested further requirements to be met by the petitioner.

On May 9, the petition was evaluated. When eight deficiencies were found, EPA requested further data. In a letter to Olin Corporation dated May 25, EPA outlined these deficiencies and stated that the toxicology review could not progress without the results of the carcinogenic and teratogenic tests in progress. On December 2, 1972, interim tolerances were established identical to the proposed tolerances. Olin proposed amendments to the petition on January 30, 1973, which were accepted on March 2, 1973.

On March 14, 1973, EPA stated that a teratology study submitted by the registrant had satisfied one of the toxicological requirements for making the proposed tolerances permanent. However, it was noted that the carcinogenicity study still had to be submitted before permanent tolerances could be recommended.

EPA informed the registrant on June 5, 1973 that only two of the deficiencies had been corrected, while six were still unresolved. It was recommended that permanent tolerances not be established. It was stated that a tolerance of 0.2 ppm for total residues of HCB, PCB and PCA would be required for meat, fat and meat by-products of cattle, goats, horses and sheep, and 0,2 ppm in milk fat. It was

stressed tht these suggested tolerances for HCB were based only on HCB arising from PCNB uses; the tolerance pending for HCB under another petition might require addition of a paragraph under 40 CFR 180.3 specifying that residues of HCB shall not exceed the higher of the two tolerances.

EPA received a progress report on the National Cancer Institute cancer bioassay on rats and mice on February 21, 1974.

On July 9, 1974, the petitioner was notified of the acceptability of protocols for chicken feeding study, and this study was received by EPA on November 17, 1975.

B. Referral to OSPR

Action was started by OSPR on the basis of the findings of Innes et al. (1969) that PCNB induced a statistically significant increase in the incidence of tumors in mice. PCNB was placed on the RPAR list in July, 1976 for action.

III. SUMMARY OF SCIENTIFIC EVIDENCE TO SUPPORT REBUTTABLE PRESUMPTION--ONCOGENICITY

40 CFR 162.11 (a)(3)(ii)(A) provides that a "rebuttable presumption shall arise if a pesticide's ingredient(s) . . . (i)nduces oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation, or dermal exposure . . . ." Section 162.3(bb) defines the term oncogenic as "the property of a substance or a mixture of substances to produce or induce benign or malignant tumor formation in living animals."

Several studies have been examined by the Agency and collectively present evidence which meets the above criterion. Briefly, these findings are that PCNB induced:

1. A significant increase in hepatic carcinomas in male mice exposed to 1000 to 3000 ppm PCNB in the diet ($p<0.021$).

2. A significant increase in fibrosarcomas of the skin in female mice at 1200 ppm in the diet ($p<0.001$).

3. A significant increase in hepatomas in male mice fed 1206 ppm in the diet ($p<0.011$).

4. A significant increase in skin papillomas in mice receiving PCNB as an initiating agent followed by croton oil applications (males, $p<0.0225$; males and females and females combined, $p<0.011$).

5. A higher occurrence of malignant lymphoreticular tumors in male rats exposed to 1200 ppm in the diet ($p<0.0548$).

Following are descriptions of the tests which resulted in these conclusions.

A. Hazelton Carcinogenesis Bioassay of PCNB

A carcinogenesis bioassay of PCNB was started in 1972 at Hazelton Laboratories, Inc. on behalf of the National Cancer Institute. The experiments used Osborne-Mendel rats (Supplier: BmI) and B6C3F1 mice (Supplier: Charles River Laboratories).

These animals were fed a mixture of corn oil and PCNB ad libitum at two dose levels, with 50 males and 50 females of each species in each group. Control groups for each species consisted of 20 animals of each sex.

The composition of the PCNB has been reported by the supplier as (Olin Corporation letter, 1976):

	weight (%)
Pentachloronitrobenzene	98.1-98.2
Pentachlorobenzene	0.11-0.16
Chloranil	0.13-0.15
2,3,4,5-Tetrachloro-nitrobenzene	0.22-0.29
Hexachlorobenzene	1.0
High Boiler (unknown)	0.30-0.22

Male rats in the low dose group received 7,500 to 5,000 ppm, and 15,000 to 10,000 ppm PCNB in the high dose group. These doses were decreased to the second dosage rate after 14 weeks and continued until feeding was completed at 78 weeks. Low dose females were fed 11,000 ppm for 14 weeks; this was decreased to 7,250 ppm PCNB for the remainder of the experiment. High dose females received 22,000 ppm for 14 weeks and 14,500 for the remainding feeding period. All animals were sacrificed after 111-113 weeks.

Mice were fed PCNB for 78 weeks. Low dose males were fed increasing doses of 1,075 ppm to 3,000 ppm, and high dose males received 2,150 to 6,000 ppm. Low dose females were fed 2,320 to 4,500 ppm and the high dose groups received 4,640 to 9,000 ppm. Surviving animals were sacrificed 91 to 93 weeks after the start of feeding.

The results obtained from rats showed a higher incidence of carcinomas in low dose PCNB-treated males and females. Female rats fed the low dose also had increases in malignant tumors. However, these observations are not statistically significant ($p<0.05$).

Carcinomas of the liver increased in low dose male mice, with eight of eighteen mice (44%) in that group, compared to two of twenty control male mice, developing carcinomas. This is significant at $p<0.021$ (Albert, 1977).

B. Central Institute for Nutrition and Food Research--Mouse Study

At the request of Farbwerke Hoechst AG (Frankfurt, W. Germany), the Central Institute for Nutrition and Food Research conducted a mouse carcinogenesis bioassay of PCNB (Van der Heijden and Til 1974). The technical grade sample contained:

	weight (%)
Pentachloronitrobenzene	98.2-98.3
Hexachlorobenzene	2.7
2,3,4,5-tetrachloronitrobenzene	1.1
2,3,5,6-tetrachloronitrobenzene and 2,3,4,6-tetrachloronitrobenzene	0.64
Chloranil	<0.5

Diet pellets were administered ad libitum to SPF (Swiss random bred) males and females in 0, 100, 400 and 1200 ppm dose groups for 80 weeks.

Gross necropsies were conducted. Tissues and tissues with gross abnormalities, three sections of the liver and each lung lobe were histologically prepared and examined. The gross examination showed skin abcesses and subcutaneous

masses in females that had ingested 1200 ppm PCNB. From tissue specimens, they were identified as fibromas and fibrosarcomas. 12 of 91 females at this dose level, compared to none of the 90 control females, had these tumors at $p<0.001$ (Albert 1977).

C. Central Institute for Nutrition and Food Research--Rat Study

In September, 1971 the Institute began a carcinogenesis test for PCNB on rats at the behest of Farbwerke Hoechst A.G. (Anonymous undated) The technical material was the same as that used in the mouse study. Males and females, 50 per dose group, were fed a diet of 0, 100, 400 and 1200 ppm for 104 weeks.

Complete gross necropsies were conducted to provide tissues for histological fixing and scrutiny. Tissue examinations were detailed for 20 males and females from the control and 1200 ppm groups, but were limited to the liver for all other animals.

26 of 47 (55%) males ingesting 100 ppm had significantly more lymphoreticular tumors of the lung ($p<0.0548$). Most of these tumors were reticulum cell sarcomas; 20 of 47 tumors were found in treated males and 8 of 44 tumors were seen in untreated males (Albert 1977).

D. Innes Mouse Study

A tumorigenicity screening study on PCNB was conducted by Bionetics Research Laboratories, Inc. from 1966-1967 for the National Cancer Institute (Innes et. al., 1969). While the purity of the sample was not reported, it is suspected that it contained about 88% PCNB and 11% hexachlorobenzene (U.S.E.P.A. 1976b).

Strain X and Strain Y mice, (C57BL-6 x C3H/Anf)F1 and (C57B1/6 x AKR)F1, respectively, were administered 464 mg/kg PCNB (maximum tolerated dose) by stomach tube at seven to 28 days of age and orally ad libitum up to necropsy at 78 weeks. There were 18 males and 18 females of each species in the control and treated groups.

Mice were grossly examined post mortem externally and in the thoracic and abdominal cavities. Tissues of major organs and of grossly visible lesions were reviewed microscopically. The cranium and thyroid glands were not dissected.

A significantly elevated incidence of liver tumors was found in the Strain Y males ingesting PCNB. 10 of 17 (59%) treated males compared to 1 of 17 (6%) of control males had hepatomas at $p<0.00246$ (Albert 1977).

E. Tumor Initiating Study in Mice

The University of Birmingham Cancer Research Laboratories in Birmingham, England has conducted a study on the tumor initiatory activity of technical PCNB (Searle, 1966). The purity of the compound was not reported.

Treated and untreated groups of albino mice (background unspecified), 6-8 weeks old, were assigned 10 males and 10 females each. The backs of mice to be treated were shaven and 0.2 ml of 0.3% PCNB dissolved in acetone was applied twice weekly for 12 weeks. These mice then received applications of croton oil on the same skin area for another 20 weeks.

Total number of tumors and the numbers of mice bearing visible skin tumors were recorded weekly during croton oil treatment, and biweekly thereafter. Papillomas less than 1 mm in diameter or persisting less than three weeks were not counted.

Mice from treated and untreated groups began to develop papillomas at the same rate during croton oil treatment. When croton oil applications ceased, however, seven treated males retained tumors as compared to only one in the control group, significant at $p<0.0225$ (CAG Report, 1977). Also, 14 of 20 treated males and females (combined), compared to 5 of 20 untreated males and females (combined), had papillomas, which is significant at $p<0.0225$.

IV. EVIDENCE NOT SUFFICIENT TO SUPPORT REBUTTABLE PRESUMPTION

A. Acute Toxicity

(1) Humans and Domestic Animals

The criteria for dermal toxicity for PCNB as formulated or diluted are not met, since the acute percutaneous LD-50 for rabbits is greater than 4 g/kg (Borzelleca 1971).

The criterion for acute toxic effects from inhalation of PCNB is not met due to lack of data.

(2) Wildlife

PCNB does not meet any of the acute criteria for hazards to wildlife as follows:

(a) Mammals

The acute oral toxicity of PCNB was determined in a test (Finnegan et. al 1958) that does not meet present-day standards. Therefore, this RPAR criterion has not been due to lack of data.

(b) Avian species

The acute oral LC-50 for bobwhite quail and mallard ducklings was determined by Calandra (1973a, 1973b). However, these tests do not meet present-day standards. Therefore, this RPAR criterion has not been met due to lack of data.

(c) Aquatic organisms

Because PCNB may not be applied directly to water and is not readily transported to water bodies, its labelled use will not cause a concentration in water sufficient to meet the RPAR criterion (McCann 1967, Bionomics 1974).

B. Chronic Toxicity

(1) Humans and domestic animals

No data has been found which meets this RPAR criterion at this time.

(2) Wildlife

No studies for PCNB or HCB show that significant population reduction in organisms could be reasonably anticipated.

C. Lack of Emergency Treatment

Since adequate first-aid treatments are available to PCNB users, the criterion in Section 162.11 (a)(3)(iii) has not been met.

V. REQUEST FOR INFORMATION

Section 162.11(a)(3)(ii)(B) states that an RPAR shall arise if a chemical "produces any other chronic or delayed toxic effect in test animals at any dosage up to a level, as determined by the Administrator, which is substantially higher then that to which humans can reasonably be anticipated to be exposed, taking into account ample margins of safety...."

While no data indicates that this criterion is met by PCNB by itself, this Agency is concerned about preliminary information which indicates that HCB may induce oncogenic and other chronic effects in test animals. Since the reports providing most of the information are not in final form, the Agency cannot determine at this time that any RPAR criteria have been met by HCB. However, when final and verified reports are obtained, they will be fully evaluated along with already published studies (Courtney 1976, Khera and Villenueve 1975, Villenueve and Khera 1975) for the possibility that grounds for an RPAR exist. If an RPAR is declared for the potential effects of HCB in PCNB, a supplemental RPAR notice may be issued in the Federal Register for PCNB. If the Agency declares an RPAR for all products containing HCB, a separate FR notice will be issued, and all PCNB registrants may respond accordingly. A summary of the information awaiting consideration follows:

A. Oncogenicity

Dr. J. R. Cabral, while previously with the Eppley Institute for Research on Cancer, University of Nebraska, has preliminarily reported that HCB induces oncogenic effects in hamsters (Cabral 1977a and 1977b).

Male and female Syrian golden hamsters were fed HCB in the diet at doses of 0, 50, 100 and 200 ppm, with 40, 30, 30 and 60 animals of each sex in each dosage group, respectively, After 80 weeks of feeding, significant increases in hepatomas were observed in HCB treated animals (low dose females, 37.5%, and males 27.2%; middle dose females, 42%, and males, 75%; high dose females, 81%, and males, 87%) compared to no hepatomas in untreated hamsters. Hemangioendotheliomas occurred significantly higher in hamsters receiving 200 ppm HCB (females, 9%, and males, 34%) than controls. Thyroid tumors were present only in treated animals and in proportion to the dose.

B. Reproductive and Other Adverse Effects

Linder et. al. (1977) are nearing the completion of a multi-generation reproductive study and some auxiliary experiments in rats. While the final results of the test are not yet available, the preliminary findings and the test design are of interest.

Technical grade hexachlorobenzene (HCB) was fed to rats at dietary concentrations of 0, 5, 20 or 100 ppm, and manifestations of toxicity observed through weaning of the third filial generation. Suckling pups of rats fed 100 ppm developed tremor and most of them died 4-14 days after birth. At weaning, liver weights of pups were increased in each filial generation of the group fed 20 ppm HCB, and, to a lesser degree, in some weanlings of the group fed 5 ppm. Significant HCB residues were found in whole fetuses and stomach contents of sucklings whose parents were fed 100 ppm HCB. Pathologic changes in the liver, consistng of hepatocellular enlargement in both sexes and slightly increased hemosiderin in females, were limited to adult rats fed 100 pm HCB. In the lungs, an increase in size, number and distribution of intraalveoiar (lipid-containing) macrophages was observed in HCB-treated rats. Porphyrin uria and excess storage of hepatic porphyrins occurred primarily in female rats fed 100 or 20 ppm HCB.

The Agency requests that any party having new or additional information on these or other potential adverse effects of PCNB or HCB submit such information for consideration in the RPAR process.

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